NUTRITION AND CANCER, 36(2), 170–176

Eating Frequency and Risk of Colorectal Cancer

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Abstract: *Case-control studies have found elevated risk of colorectal cancer with higher eating frequency. The present analyses, the first to examine this association using prospectively collected information, utilized nationally representative data from the Epidemiologic Follow-Up Study of the First National Health and Nutrition Examination Survey (NHEFS). The study population included 9,978 subjects followed from 1982–84 to 1992. Colorectal cancer cases (n = 141) were identified by self-report, hospital records, and death certificates. Interviews conducted in 1982–84 provided information on meal and snack frequencies and covariates of interest. Relative risk (RR) of colorectal cancer and 95% confidence intervals (CI) were estimated using Cox proportional hazards models adjusted for age, gender, and race and energy, alcohol, total fat, and fiber intake. Compared with those eating <3 times/day, those eating 3–4 times/day had an RR of 0.66 (95% CI = 0.42–1.03) and those eating >4 times/day had an RR of 0.74 (95% CI = 0.41–1.32). The association was due to decreased risk with more meals rather than more snacks per day. Given limitations of previous studies as well as the possibility of a protective effect of higher eating frequency through improved glycemic control, the present findings suggest that the influence of eating frequency on colorectal cancer risk is more complex than has been previously supposed and merits additional study.*

Introduction

An increased frequency of eating has been hypothesized to increase risk of colon cancer by increasing secretion of bile acids into the gut lumen (1). Deconjugation and dehydroxylation of these bile acids by colonic bacteria produce secondary bile acids, which may have tumorigenic effects (2,3). Alternatively, increasing eating frequency can also be hypothesized to decrease risk of colon cancer. An eating pattern of "nibbling" rather than "gorging" may improve glycemic control (4), reducing postprandial hyperinsulinemia and its stimulatory effects on colon tumors (5). Six case-control studies have reported on the association between eating frequency and risk of colon cancer (1,6–10); all six showed a slightly greater risk with higher frequency of eating occasions. The objective of these analyses was to examine the association between eating frequency and risk of colon and rectal cancers by using prospective data from the Epidemiologic Follow-Up Study of the First National Health and Nutrition Examination Survey (NHANES I).

Materials and Methods

Study Population

The study population included participants in the NHANES I Epidemiologic Follow-Up Study (NHEFS). NHANES I, conducted between 1971 and 1975, used a multistage sample design to obtain a national probability sample of the noninstitutionalized civilian population of the United States, excluding Alaska, Hawaii, and Native American reservation lands (11,12). The elderly, women of child-bearing age, and persons residing in poverty areas were oversampled. About 70% of those targeted were interviewed and medically examined in NHANES I. NHEFS was a longitudinal study of the 14,407 participants between the ages of 25 and 74 years at the time of the initial survey and was undertaken to investigate the effects on morbidity and mortality of various factors assessed at baseline (13–16). Follow-up took place in 1982–84, 1986, 1987, and 1992. The 1986 follow-up was conducted only among subjects aged ≥55 years at the NHANES I examination. During each follow-up, subjects or their proxies were interviewed. Also, health records were obtained for instances in which participants reported an overnight stay in a health care facility between the participant's baseline examination and last follow-up visit. Death certificates were obtained for deaths during the follow-up period and were identified by the National Death Index or other tracing mechanisms. Health records were obtained for >70% of

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reported overnight stays, and death certificates were obtained for 99% of deaths between 1971–75 and the 1992 follow-up (16). Information on eating frequency was obtained only in the 1982–84 questionnaire; thus 1982–84 served as the baseline for these analyses.

Of the 14,407 NHEFS participants, 1,024 could not be traced, 2,022 died before the 1982–84 interview, and 838 were not interviewed in 1982–84, leaving 10,523 persons interviewed in 1982–84, 253 of these with proxy interview data. Of these, the following were excluded from the study population: subjects with a diagnosis of colon or rectal cancer at or before the 1982–84 interview ($n = 94$), subjects not followed after the 1982–84 interview ($n = 221$), subjects missing meal or snack frequency information ($n = 229$), and subjects who reported total eating frequency of zero ($n = 1$). This left 9,978 subjects available for analysis.

Assessment of Eating Frequency

Eating frequency was assessed in the 1982–84 interview by use of the following questions: "Including evening snacks, how many between-meal snacks do you have per day?" and "How many meals do you usually eat a day?" The terms "meals" and "between-meal snacks" were not further defined for participants. Three measures of eating frequency were examined: meal frequency, snack frequency, and total eating frequency, calculated as the sum of meals and snacks eaten per day. Meal frequency was categorized as <3 or ≥3 meals/day. Snack frequency was categorized as <1, 1, and >1 snack/day. Total eating frequency was categorized as <3, 3–4, and >4/day. Categories were selected on the basis of the distribution of each measure in the study population, ensuring adequate numbers in each group.

Diagnosis of Disease

Incident cases of colorectal cancer met at least one of the following criteria: 1) report by subject (or proxy) of a first diagnosis of colon or rectal cancer at any of the follow-up interviews conducted in 1986, 1987, or 1992, 2) one or more hospital stays during the follow-up period with a discharge diagnosis coded 153.0–153.4, 153.6–153.9, or 154.0–154.1 according to the International Classification of Diseases, Ninth Revision, Clinical Modification, and 3) a death certificate with underlying or nonunderlying cause of death coded as any of the International Classification of Diseases codes given above. Where self-reported information and hospital records or death certificates differed with respect to type of cancer or date of diagnosis, data from the hospital records or death certificates were used. Between 1982–84 and 1992, there were 150 incident cases of colorectal cancer, of whom 55% were identified as cases by at least two sources (self-report, hospital records, and/or death certificate data). Of 35 (23%) cases who were self-reported but unconfirmed by hospital records or death certificate data, 14–21 cases were unconfirmed for logistical reasons, for example, the health facility failed to respond to requests for abstracts.

Assessment of Covariates

Information on all covariates was taken from responses to the 1982–84 interview. Covariates of interest as potential confounders or effect modifiers in these analyses were age, gender, race, family history of colorectal cancer, energy intake, intake of alcohol, total fat, dietary fiber, red meat, and fruits and vegetables, body mass index, measured as weight (in kg) divided by height (in m^2), recreational physical activity, activity levels apart from recreation, regular aspirin use, smoking at the time of the 1982–84 interview, pack-years of exposure at that time, smoking 35 years before the interview, and pack-years of exposure 35 years in the past. We used smoking 35 years ago to take into account the possibility of latency of a smoking effect (17).

Information on frequency of red meat and fruit and vegetable intake was obtained from a food frequency questionnaire with approximately 100 items, administered in the 1982–84 interview. Red meat intake was estimated as the sum of reported intake of beef, roast pork or pork chops, and fresh ham or spare ribs. Fruit and vegetable intake was based on response to a question that asked about intake of fruits and vegetables of all kinds, including fresh, canned, dried, frozen, cooked, raw, or juices. Energy, total fat, and fiber intake were estimated on the basis of frequency of consumption information from the same questionnaire, along with representative gender- and age-specific portion size information from NHANES II (18).

Statistical Analysis

Follow-up time was calculated by subtracting date of 1982–84 interview from last date known to be alive and free of colorectal cancer (date of last interview, contact, or death) for noncases or from date of colorectal cancer diagnosis for cases. For cases identified from death certificate data, date of 1982–84 interview was subtracted from date of death.

Adjusted relative risk (RR) of colorectal cancer was estimated using Cox proportional hazards models. Before modeling, the assumption of proportional hazards was tested by examining log-log survival curves and by including time-dependent variables in the Cox models. We found no substantial departures from the proportional hazards assumption, and thus subsequent models did not include time-dependent variables.

All models included age at the 1982–84 interview (in single years), gender, and race (black, nonblack). Fully adjusted models also included intake of energy (≤1,160.0, >1,160.0–1,877.9, ≥1,878.0 kcal/day), alcohol (0, >0–0.5, ≥0.5 drink/day), total fat (≤41.0, >41.0–70.9, ≥71.0 g/day), and fiber (≤10.0, >10.0–16.9, ≥17.0 g/day). Categories for energy, total fat, and fiber intake represented the 0 to 25th, 25th to 75th, and 75th to 100th percentiles of intake. In addi-

tional models, we replaced total fat and fiber variables with variables representing intake of red meat (≤2.0, >2.0–5.9, ≥6.0 servings/wk) and fruits and vegetables (≤1.0, >1–2.9, ≥3.0 servings/day). Other variables of *a priori* interest as potential confounders, including physical activity, body mass index, regular aspirin use, and smoking, were not included in final models, because they were uncorrelated with exposure and outcome in crude bivariate analyses or because removing them from initial models did not meaningfully change estimates for risk associated with eating frequency. Results are presented including all subjects not missing any variables included in the fully adjusted model ($n = 9,729$). Tests for linear trend in the RR for categories of snack and total eating frequencies were conducted by fitting a model with a variable representing the median value for each category while adjusting for other covariates.

To address the possibility that type of diet, for example, diets high in fat or low in fruits and vegetables, modifies the effect of eating frequency in these data, bivariate analyses were stratified on intake of total fat, dietary fiber, red meat, and fruits/vegetables. Also, proportional hazards models were run, including interaction terms, with each potential effect modifier, with adjustment for age, gender, and race. In stratified analyses and proportional hazards modeling, each potential effect modifier was dichotomized by dividing at the approximate median level of intake for each in the baseline population. Because neither stratified analyses nor modeling with interaction terms showed meaningful effect modification of total eating frequency by intake of these factors, no interaction terms were included in final models.

Additional analyses were performed 1) excluding 33 self-reported cases without hospital or death certificate confirmation, 2) excluding 1,233 subjects who may have altered their eating patterns for reasons related to colorectal cancer risk, specifically, those with a history of ulcerative colitis or cholecystectomy, 3) excluding 552 subjects with prior diagnosis of any cancer except nonmelanoma skin cancer, and 4) using age rather than time on study as the time scale (19). Results from these analyses were similar to those from the main analyses (not shown).

To assess the effect of the complex survey design on results, Cox proportional hazards regression analyses were performed using PROC SURVIVAL in SUDAAN (20). The results derived from the unweighted analyses were consistent with those derived from analyses incorporating the complex survey design; thus only unweighted results are presented here.

Results

Of the 9,978 persons available for analysis, 63% were women and 13% were black. Mean age at the 1982–84 interview was 58 years. Between 1982–84 and 1992, there were 150 incident cases of colorectal cancer, which included 110 cases of colon cancer, 16 cases of rectal cancer, and 24 cases with cancer at both sites.

Table 1. Distribution of Meals, Snacks, and Total Eating Frequency in 9,978 Participants in the National Health Examination Follow-Up Study, 1982–1992

Variable	Number (%)
Meals/day	
<3	4,043 (40.5)
3	5,875 (58.9)
4–8	60 (0.6)
Snacks/day	
<1	3,219 (32.3)
1	4,134 (41.4)
2–20	2,625 (26.3)
Total eating frequency/day[a]	
<3	1,477 (14.8)
3–4	6,628 (66.4)
5–22	1,873 (188)

a: Calculated as sum of meals and snacks per day.

About 60% of the subjects had ≥3 meals/day, and about 66% had a total eating frequency of 3–4 times/day (Table 1). Examination of bivariate and multivariate associations was conducted only among 9,729 of 9,978 subjects with complete covariate data, including 141 of 150 colorectal cancer cases. More-frequent eaters (sum of meals and snacks per day) were more likely to be nondrinkers, to consume red meat, fruits, and vegetables more frequently, and to have higher intake of total fat, dietary fiber, and energy (Table 2).

Having ≥3 meals/day was associated with a nonsignificantly decreased risk of colorectal cancer relative to having <3 meals/day, whereas risk of colorectal cancer was not associated with number of snacks (Table 3). The inverse association between meal consumption and colorectal cancer risk appeared to drive the decreased risk associated with a total eating frequency of ≥3 times/day (Table 3).

Adjusting for intake of red meat and fruits/vegetables instead of total fat and fiber intake did not change RR estimates for total eating frequency (results not shown). Total eating frequency was not associated with rectal cancer when we examined colon cancer and rectal cancer cases separately (RR = 1.18, 95% confidence interval = 0.12–9.07 for total eating frequency of >4 vs. <3/day), although the number of rectal cancer cases included in this analysis was small ($n = 14$).

Discussion

We found some suggestion of decreased risk of colorectal cancer with total eating frequency of ≥3 times/day. The suggested inverse association between total eating frequency and colorectal cancer appeared to be due to the lower risk associated with consuming ≥3 meals/day as opposed to <3 meals/day. There was no apparent association between colorectal cancer and number of snacks per day, nor did the relationships vary according to type of diet, as characterized by intake of total fat, fiber, red meat, and fruits and vegetables.

Table 2. Distribution of Covariates by Level of Total Daily Eating Frequency in 9,729 Participants in the National Health Examination Follow-Up Study, 1982–1992[a]

	Total Daily Eating Frequency[b]		
	<3 (n = 1,421)	3–4 (n = 6,489)	>4 (n = 1,819)
Mean age, yr	54.9	58.3	56.5
Percent women	63.8	61.9	65.0
Percent black	18.4	11.7	12.0
Percent consuming alcohol at			
0 drinks/day	36.4	43.3	47.7
>0 to <0.5 drink/day	41.8	42.5	41.7
≥0.5 drink/day	21.8	14.2	10.7
Percent consuming red meat at			
≤2.0 servings/wk	25.3	20.8	18.1
>2.0–5.9 servings/wk	52.6	54.6	53.1
≥6.0 servings/wk	22.0	24.6	28.9
Percent consuming fruits and vegetables at			
≤1.0 serving/day	40.4	24.1	18.8
>1–2.9 servings/day	37.6	38.0	33.5
≥3.0 servings/day	22.0	37.9	47.8
Percent consuming total fat at			
≤41.0 g/day	37.7	25.4	13.0
>41.0–70.9 g/day	45.9	51.0	49.3
≥71.0 g/day	16.5	23.6	37.7
Percent consuming fiber at			
≤10.0 g/day	40.8	24.8	16.6
>10.0–16.9 g/day	42.9	50.0	47.9
≥17.0 g/day	16.3	25.2	35.5
Percent consuming energy at			
≤1,160.0 kcal/day	38.4	25.3	13.3
>1,160.0–1,877.9 kcal/day	43.6	51.6	49.0
≥1,878.0 kcal/day	18.0	23.1	37.7

a: Only subjects not missing information on any of the covariates listed are included.
b: Total eating frequency was calculated as sum of meals and snacks eaten per day.

Table 3. RR and 95% CI for Eating Frequency and Colorectal Cancer in 9,729 Participants in the National Health Examination Follow-Up Study, 1982–1992[a]

	No. of Cases	Person-Years Follow-Up	Minimally Adjusted RR[b] (95% CI)	Fully Adjusted RR[c] (95% CI)
Meals/day				
<3	53	33,113	1.0 (ref)	1.0 (ref)
≥3	88	46,523	0.71 (0.50–1.01)	0.74 (0.52–1.07)
Snacks/day				
<1	53	24,732	1.0 (ref)	1.0 (ref)
1	60	33,705	1.08 (0.74–1.56)	1.11 (0.76–1.62)
>1	28	21,199	0.93 (0.58–1.47)	0.98 (0.61–1.57)
Trend P value[d]			0.83	0.98
Total eating frequency/day				
<3	26	11,744	1.0 (ref)	1.0(ref)
3–4	91	53,049	0.62 (0.40–0.96)	0.66 (0.42–1.03)
>4	24	14,843	0.68 (0.39–1.18)	0.74 (0.41–1.32)
Trend P value[d]			0.42	0.61

a: Abbreviations are as follows: RR, relative risk; CI, confidence interval; ref, referent.
b: Adjusted for age, gender, and race.
c: Adjusted for age, gender, race, energy intake, and intake of alcohol, total fat, and fiber.
d: P value for trend was estimated by fitting coefficient to an ordinal variable representing median frequency for each category.

The six previous studies that examined the relationship between eating frequency and risk of colorectal cancer, all case-control in design, found increased risk with increased eating frequency (1,6–10). In the first study to report an association between eating frequency and colorectal cancer risk, a population-based study conducted in Adelaide, Australia, Potter and McMichael (1) found that eating ≥5 meals/day was associated with a 60–70% greater risk of colon cancer than eating ≤3 meals/day; meal frequency was not associated with rectal cancer risk. A population-based study in Majorca, Spain, conducted by Benito and co-workers (7) showed a twofold greater risk of colon cancer for ≥4 than for ≤3 meals/day. In a population-based study in Stockholm, Sweden, de Verdier and Longnecker (8) found that risk of colon cancer increased with greater eating frequency, such that eating >5 times/day was associated with a twofold greater RR than eating ≤3 times/day; risk specifically increased in relation to greater snack frequency, whereas it was unrelated to meal frequency. A hospital-based study in Northern Italy by Franceschi and co-workers (9) showed a twofold greater risk of colon and rectal cancers for ≥4 than for ≤2 meals/day. Two studies in the United States were conducted using Wisconsin's statewide cancer registry. The earlier study by Young and Wolf (6) showed a 30% greater risk of colon cancer for 5 than for 2 meals/day. In a more recent study conducted only among women in Wisconsin, Shoff and colleagues (10) found a 40% greater risk of colorectal cancer for 3–4 than for 1–2 meals/day but no association with snack or total eating frequency.

Inconsistencies in various aspects of previous studies, however, complicate an overall interpretation of their findings. While the Stockholm study found that higher risk was associated specifically with frequency of snacks rather than meals (8), for example, the study on Wisconsin women (10) showed increased risk with more meals and not snacks. The magnitude of the association also varied across studies. Although the Majorca (7), Stockholm (8), and Northern Italy (9) studies showed twofold differences in risk within limited ranges of eating frequency, the Adelaide (1) and Wisconsin (6) studies showed weaker associations or associations only at relatively high (≥5/day) consumption frequencies.

The discrepant results of this study may arise because the categories used in the present study are not sensitive enough to reveal a significant positive association between eating frequency and colorectal cancer risk. More specifically, five of the six previous studies found an increase in risk with ≥4 meals/day, whereas we compared ≥3 with <3 meals/day. Thus risk may not increase until ≥4 meals/day are attained. In our study, too few individuals reported eating >3 meals/day to evaluate it as a separate category, and the possibility that risk does in fact increase in this category cannot be excluded. It should be noted, however, that two of three previous studies (8–10) reporting on this did not find evidence for a threshold effect at >4 meals/day but found an increase in risk even for individuals consuming 3 meals/day (9,10).

The discrepancy in findings between present and previous analyses may also be attributable to how meal and snack frequencies were assessed. Although studies by Franceschi and associates (9) and Shoff and others (10) specifically excluded low-calorie beverages (e.g., coffee, tea, and water), eating frequency in all studies was estimated by the study participants themselves, and meals and snacks were self-defined. The quality of self-reported information on meal and snack frequencies is unknown. Reporting of meal and snack frequencies, however, is influenced by cultural values (e.g., the acceptability of snacking) and by culturally influenced perceptions (e.g., eating with others as a defining aspect of a meal vs. a snack) (21). In comparing the present analysis with previous studies, it is notable that previous studies were conducted in relatively small, primarily European-origin populations in Europe, Australia, and the United States, whereas the present study is the first to include individuals from throughout the United States, including a larger proportion of black participants. Although it is unclear how cultural differences might have biased associations in either direction, cultural differences in reporting meal and snack occasions as well as in the actual nature and content of the meal or snack render comparisons across study populations difficult. Interestingly, total eating frequency in this study population [3.6 ± 1.2 (SD)] was similar to that observed (3.5 ± 0.9) in the 1987–1988 Nationwide Food Consumption Survey, another population of individuals from throughout the United States (22).

Differences in referent period are unlikely to have contributed to the discrepant findings between our study and previous studies. Several of the previous case-control studies (1,9,10) were based on recent intake (up to 2 yr before diagnosis), whereas average length of follow-up in the present study was eight years. Nevertheless, of two previous studies based on intake further back in time, i.e., the Stockholm study (8) based on intake up to five years before diagnosis and the Wisconsin study (6) based on intake as far back as before 18 and between 18 and 35 years of age, both found increased risk of colorectal cancer with greater frequency of eating.

A higher frequency of eating was previously hypothesized to increase risk for colon cancer by increasing secretion into the intestinal lumen of bile acids, which may be metabolized by colonic bacteria to produce secondary bile acids with potentially tumorigenic effects. Interestingly, there is also a biological reason to expect higher eating frequency to decrease risk for colon cancer. Increased eating frequency has been associated with dampened glucose and insulin responses postprandially, reflecting slowed carbohydrate absorption and a more controlled insulin response (4). Indeed, increasing eating frequency, or nibbling as opposed to gorging, has been suggested as a means of improving glycemic control in patients with diabetes (4). Reduced postprandial hyperinsulinemia resulting from improved glycemic control may reduce risk for colon cancer, because insulin is a mitogen to colon cancer cells (5). Furthermore, at patho-

physiological levels, insulin can activate insulin-like growth factor I receptors, also increasing tumor cell proliferation in the colon (5).

If the nibbling pattern is defined as spreading a given intake load over several eating occasions as opposed to eating a comparable amount all at once, then this biological mechanism provides a possible explanation for the observation that risk was inversely associated with meals but not snacks. In our data, meal frequency may have reflected the nibbling pattern more accurately than snack frequency, as suggested by the fact that caloric intake was only weakly associated with number of meals (Pearson $r = 0.10$) but more strongly increased with number of snacks ($r = 0.20$). Indeed, increased eating frequency that does not reflect a true nibbling pattern, namely, eating more in the process of eating more frequently, may increase risk not only by increasing colonocyte exposure to secondary bile acids, but also by increasing exposure to postprandial insulin peaks (5). Clearly, the potential effects of meal patterns on colorectal cancer are complex, and improved methods of assessing meal patterns will be required for future studies.

A limitation of our study was that a relatively large proportion of self-reported cases was unconfirmed by hospital record or death certificate data, although a sensitivity analysis excluding unconfirmed cases produced results similar to the analysis based on the full case population. Residual confounding was also possible if the dietary factors that were controlled for were poorly measured in the survey and if more-frequent eaters in our study population tended to consume a diet protective against colorectal cancer. However, there was no evidence of substantial confounding in our data. In addition, none of three previous studies that also adjusted for energy intake (1,8,9), fat, protein, and fiber (8), or red meat (9) in their analyses found notable confounding by these variables. Another possible source of uncontrolled confounding is physical activity, which was crudely measured in NHEFS, although additional adjustment for physical activity in the Stockholm study also showed no notable confounding (8).

Although higher frequency of eating may increase risk only in conjunction with certain types of diets, we found no evidence of effect modification or of increased risk in high fat, high red meat, low fiber, or low fruit/vegetable strata. The Northern Italy study also stratified on intake of red meat and found no evidence of effect modification (9).

A significant advantage of this study over previous studies is that it was based on prospective data, whereas all previous studies were retrospective in design. Diagnosis and treatment of colorectal cancer in previous studies may have caused some subjects to alter their frequency of eating, thereby influencing their recall of eating patterns before disease occurrence (23).

In summary, these results, based on prospective data, do not confirm an association between eating frequency and increased risk of colorectal cancer found in previous case-control studies. Despite the apparently consistent findings of previous studies, interpretation of their results is limited by potentially biased case responses and by inconsistencies when details of the association with eating frequency are evaluated. Our finding of an inverse association between eating frequency and colorectal cancer risk is biologically plausible because of potential protection against hyperinsulinemia. Finally, although a better understanding of the effects of eating frequency on colorectal cancer risk is potentially useful for disease prevention, it should be emphasized that eating frequency, whether examined for etiological or for prevention purposes, cannot be considered apart from the content and quality of what is eaten.

Acknowledgments and Notes

The authors thank Dr. Barry Graubard for assistance with this analysis and Drs. Dale Sandler and Glinda Cooper for comments on the manuscript. Address reprint requests to M. Tseng, Div. of Population Science, Fox Chase Cancer Center, 7701 Burholme Ave., Philadelphia, PA 19111.

Submitted 27 August 1999; accepted in final form 8 November 1999.

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